Effects on the Liver of Chemicals Encountered in the Workplace

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The liver plays a central role in toxicology. It is the primary organ of detoxification and elimination by metabolism of many chemicals. Many workplace chemicals can affect the liver in animals; fewer have been proved to do so in humans. The diverse hepatic effects observed in humans from occupational exposure to chemicals range from fatty infiltration, acute hepatitis and cholestasis to cirrhosis and angiosarcoma. Three important workplace chemicals, prototypes for the toxicities of many others, are carbon tetrachloride, vinyl chloride and the polychlorinated biphenyls (PCB's). These three are described in some detail to highlight principles of occupational toxicology. Most of the hepatic effects produced by chemicals in the workplace have clinical, laboratory and morphological features common to many other forms of liver disease. Therefore, only an astute physician who takes an occupational history will recognize the association between a patient's workplace and liver disease.

The path to diagnosis of hepatic injury produced by a chemical in the workplace is not straight. Apart from instances when a chemical produces a specific lesion, hepatic injuries produced by chemicals do not have unique clinical, laboratory or morphologic features. Toxic hepatitis, cirrhosis, portal hypertension and hepatocellular carcinoma are found with such frequency in the general population that an association between these lesions and an occupational chemical is either not recognized or difficult to prove. Clinical manifestations of acute or chronic liver diseases are often not specific enough to allow diagnosis of the cause. Furthermore, the laboratory examinations that we carry out to test liver "function" are not specific and are usually not sensitive. One laboratory test, serum γ-glutamyl transpeptidase (GGTP) activity, is more sensitive to acute hepatic damage than other serum enzyme studies. However, GGTP activity increases in the presence of many other diseases and also after consumption of drugs and alcohol, so this index must be interpreted carefully. Histologic examination of biopsy specimens may be useful to test other organs or tissues, but liver biopsy, because it is invasive, is done rarely in asymptomatic or mildly symptomatic workers. In addition, most histologic features are commonly caused by many toxins. Epidemiologic studies that can associate workplace chemicals with hepatic changes not only require large cohorts of workers but also are difficult to carry out—particularly prospective studies. Epidemiologists must match the exposed population to the control population for factors such as alcohol and drug intake, previous liver disease and life-style. All of these factors could produce hepatic injury not related to the chemical or enhance the hepatic effects of the chemical being studied.

That an individual patient's liver disease is related to the workplace will only be recognized by a physician who understands the significance of the patient's job. The medical history of any patient with liver disease should include a complete history of previous and current occupations and potential exposure to chemicals. In this review I will discuss some concepts fundamental to the understanding of the effects of chemicals on the liver.

The liver plays a central role in toxicology. Lipophilic chemicals that the body encounters are usually elimi-

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ABBREVIATIONS USED IN TEXT

CCl_4 = carbon tetrachloride
GGTP = γ-glutamyl transpeptidase
NIOSH = National Institute for Occupational Safety and Health
OSHA = Occupational Safety and Health Administration
PCB = polychlorinated biphenyl

nated at least in part by the liver through one or more metabolic steps. Metabolism usually detoxifies a potential toxin but can "activate" many important chemicals by metabolizing them to active forms, often more toxic than the parent chemical. The liver is the first organ after the gastrointestinal tract that is exposed to an ingested chemical. Therefore, concentrations in blood entering the liver are higher than those encountered by any other organ. Consequently, the liver's potential for injury by the chemical is greater.

The liver shows a marvelous diversity in the chemicals it can eliminate, which range from elements such as phosphorus and arsenic to polyhalogenated complex molecules such as the pesticide chlordecone or such widespread environmental contaminants as polyhalogenated biphenyls. As will become evident in this review, the "responses" of the liver to exposure to these chemicals are also numerous, diverse and as fascinating as normal liver "function."[1] The hepatic responses range from fatty infiltration to cell death and necrosis, from metabolic changes such as proliferation of the smooth endoplasmic reticulum to porphyrias, from infiltration by granulomas to cirrhosis, from the vascular lesion of peliosis hepatitis to angiosarcoma and from parenchymal cell adaptation to neoplasia. One chemical may produce more than one response in the liver with the type of response often determined by factors such as dose, age, route of exposure, exposure to other chemicals or drugs, presence or absence of liver disease and inherent sensitivity of the exposed person to the chemical.

Thousands of the chemicals currently in use in the workplace can produce hepatic injury in animals. Fewer have produced hepatic injury in humans. Some occupational chemicals that can affect the liver are listed in Table 1.[2] The list includes some compounds that have only been evaluated in animals. The number of occupations involved even in the use of one chemical can be large. For example, allyl alcohol is used by manufacturers of acrolein, allyl ester, drugs, fungicides, glycerine, herbicides, organic chemicals, plasticizers and resins. Xylene is used in many capacities in the occupations listed in Table 2. However, workers in these occupations not only use xylene but also a variety of other chemicals that are potentially hepatotoxic or can interact with each other to produce hepatic injury. Listed in Table 3 are the more important workplace chemicals that have affected the liver in humans, some occupations in which they are used and the hepatic responses to them. In this review the hepatic effects in humans of three chemicals that can be regarded as prototypes of a number of other compounds and illustrate many of the concepts fundamental to understanding the effects of chemicals on the liver will be examined.

TABLE 1.—*A List of Workplace Chemicals That Have Produced Hepatic Effects in Animals or Humans, or Both*[2]

2-Acetylaminofluorene	Ethyl silicate
Allyl alcohol	Fluoroalkenes
Antimony	Gasoline
Arsenic	Germanium tetrachloride
Arsine	Hydrazine
Benzyl chloride	Iron pentacarbonyl
Beryllium	Mercaptans
Bipyridyl	Metal carbonyls
Boron hydride	Methyl chloride
Cadmium	4,4-Methylenebis (2-chloroaniline)
Carbon disulfide	Nickel
Carbon tetrachloride	Nitrobenzene
Chlorinated benzenes	Nitroparaffins
Chlorinated naphthalenes	n-Nitrosodimethylamine
Chlorodiphenyls	Phenol
Chloroform	Phosphine
Chromium	Phosphorus
Cresol	β-Propiolactone
1,2-Dibromoethane	Propylene dichloride
1,2-Dichloroethane	Pyridine
Dimethyl acetamide	Selenium
4-Dimethylaminoazobenzene	Tetrachloroethane
Dimethylformamide	Tetrachloroethylene
Dinitrobenzene	Tetryl
Dinitrophenol	Thallium sulfate
Dioxane	1,1,2-Trichloroethane
Diphenyl	Trichloroethylene
Epichlorohydrin	Uranium
Ethanolamine	Vinyl chloride
Ethylenediamine	Xylene
Ethylene glycol ethers	
Ethyleneimine	

Carbon Tetrachloride

Carbon tetrachloride (CCl_4) is used either in a chemically pure grade or a technical grade (which contains other chlorinated hydrocarbon impurities). It is a colorless liquid that is volatile (vapor pressure is 91.3 mm at 20°C) and decomposes to the irritant gas phosgene in the presence of small amounts of water and heat (greater than 250°C). A quantity of 1 ppm is equivalent to 6.3 mg per cu meter. Carbon tetrachloride was synthesized first in 1839. Several reviews of its use and toxicity are available.[3-6] It was introduced as an anesthetic agent in 1847, an analgesic in 1867, a shampoo in 1909 and anthelmintic drug in 1921. Industrial production began on a large scale in the United States in about 1907, and production of this chemical was about 4.5 million kg annually in 1914, reaching 390 million kg by 1976. The compound is used primarily for synthesis of fluorocarbons but it is also a solvent, degreaser, raw material for organic chemical synthesis and a fire extinguisher. Carbon tetrachloride, used as a spot remover in the fabric care industry and at home, was banned in the United States on November 11, 1970, by the Food and Drug Administration. In the United States the Occupational Safety and Health Administration's (OSHA) standards require that an employee's exposure to CCl_4 at no time exceed a time-weighted average of 65 mg per cu meter (10 ppm) in any eight-hour shift over a 40-hour work

TABLE 2.—*A Partial List of Occupations in Which Exposure to Xylene May Occur*

Adhesive materials workers
Aviation gasoline workers
Benzoic acid makers
Cleaning fluid makers
Histology technicians
Laboratory technicians
Lacquer and varnish workers
Leather workers
Organic chemists
Paint and glue workers
Phthalic anhydride makers
Polyethylene terephthalate film makers
Quartz crystal oscillator makers
Refinery workers
Semiconductor industry workers
Solvent materials workers
Synthetic textile makers
Terephthalic acid makers

week. However, the United States National Institute for Occupational Safety and Health (NIOSH) has recommended that the 10-ppm figure be reduced to 2 ppm.[7]

Carbon tetrachloride is found in the environment. Air samples in 42 locations in the Los Angeles basin contained an average of 1.4 μg per cu meter (0.22 parts per billion).[8] The compound has been found in rivers, lakes, drinking water and effluent water from commercial manufacturing sites and from sewage treatment plants. Tolerable residue levels have been established for crops and foods: for example, in raw cereals, 50 ppm; in milled cereal products to be used for baking, 10 ppm.

The mechanisms of the hepatotoxicity of CCl_4 have been examined carefully in animals.[9-14] These studies have not only described the pathophysiology of the hepatic injury but also have led by extrapolation to a knowledge of the mechanisms of toxicity of many other compounds. The extent of injury depends more on the dose of CCl_4 than on the sensitivity of the person exposed, and can be reproduced in many species. The characteristic pathologic feature in the liver is centrilobular necrosis. The injury that leads to cell death and the necrosis. The injury that leads to cell death and the process of necrosis (conversion of dead cells to debris) follows the metabolism of CCl_4 by cytochrome P-450-dependent monooxygenases in the centrilobular liver cells. As one chlorine atom or more are cleaved from the intact molecule during metabolism, electron-deficient and, therefore, electrophilic, reactive intermediates or free radicals are produced. If not scavenged by further metabolism or conjugation, the reactive metabolites can bind covalently to a number of critical molecules and either interfere with vital cell functions or cause lipid peroxidation of cell membranes, or both. Metabolic alterations in the liver cell that result from administering CCl_4 to rats include increased fat deposition, reduced rate of amino acid utilization, decreased membrane phospholipid exchange, altered mitochondrial respiration, depressed intracellular concentrations of adenosine triphosphate and increased cellular calcium content.

The cytochrome P-450-dependent monooxygenase system found in many organs consists of a number of different forms of cytochrome P-450, each with different substrate specificities.[15] The P-450's are distributed differently throughout the liver cell lobule. The relative localization of CCl_4 toxicity to the centrizonal area of the liver cell lobule presumably relates to the presence of a larger amount of a form of P-450 that metabolizes CCl_4 in this zone than in other zones.[16] The cytochrome P-450-dependent monooxygenases are part of an extremely dynamic system and their activity changes with a large number of endogenous and exogenous variables:[17] gender, age, diet, hormonal status, genetic, diurnal and pathophysiologic factors (such as liver disease), and effects of drugs and chemicals that can enhance or inhibit the activity of the monooxygenases. For example, rats pretreated with a low protein diet or inhibitors of P-450 metabolism are much less susceptible to the hepatotoxic effects of CCl_4 than those pretreated with compounds such as phenobarbital, that enhance P-450 metabolism.[18]

One fascinating aspect of CCl_4-induced hepatotoxicity in animals is the protection that a small nonlethal dose of the compound provides to an animal from the toxicity of a subsequent dose.[19] The protection may arise from suicidal inactivation of the P-450-dependent monooxygenase during its initial metabolism of CCl_4 and its subsequent inability to "activate" the second dose. Whether or not humans exposed chronically to CCl_4 or to other similar solvents are "tolerant" to repeated doses is not known.

Because continuous exposure of animals to CCl_4 results in hepatic cirrhosis, this compound provides a model for examining the effects of chronic hepatic injury in animals.[20] The compound also produces both benign and malignant liver tumors after oral or subcutaneous administration and inhalation. Presumably, reactive intermediates bind covalently to information-carrying molecules such as DNA, RNA or protein, the reactions involved in the initiation of carcinogenesis.

In humans, CCl_4 has produced hundreds of poisonings and fatalities after occupational exposure, suicidal ingestion or medical use of the chemical.[3,5,6] Most cases arose from the inhalation of the compound in workplaces where CCl_4 was used as a solvent or dry-cleaning agent. However, CCl_4 is absorbed through both the lungs and the skin. Stewart and Dodd[21] immersed volunteers' thumbs in CCl_4 for 30 minutes: the subjects exhaled concentrations of 3 mg per cu meter (0.64 ppm), and the expiration half time was about two hours. These data highlight the general principle that in the workplace both the lungs and the skin are major routes of absorption of chemicals. Ingestion is a less important route in the workplace unless food or cigarettes are contaminated.

The clinical sequence in CCl_4-induced poisoning is shown in Figure 1.[22] The acute effects on the central nervous system (dizziness, headache, confusion and coma) reflect the anesthetic properties of the haloalkanes or haloalkenes of which CCl_4 is an example. Gastrointestinal symptoms can occur after inhalation or dermal or oral exposure. In persons exposed to high

enough concentrations of CCl_4 to produce hepatic injury, anorexia, vomiting and malaise also develop between 2 and 24 hours after the exposure. Within that time, the liver and spleen may become palpable and extremely tender because of rapid enlargement. The patient may complain of pain in the right and left upper quadrants of the abdomen. Serum aminotransferase (transaminase) concentrations and prothrombin time rise as the clinical manifestations of hepatic injury develop. After 24 to 48 hours, sequelae of acute liver failure, such as hypoglycemia and encephalopathy, may appear. Concurrently, renal failure may develop. The renal abnormalities may result from the toxic effect of CCl_4 on renal tubular cells or from "functional" renal failure that accompanies acute liver failure.[6,23] If supportive measures can keep the patient alive until hepatic

TABLE 3.—*A Partial List of Important Chemicals, Their Use in the Workplace, and the Hepatic Responses Reported in Humans*

Chemical	*Uses*	*Hepatic Responses*
Arsenic and inorganic salts	As pesticides and alloys; in production of dyes, ceramics, drugs, fireworks, paint, petroleum, ink and semiconductors	Acute injury and death of parenchymal cells; cirrhosis; angiosarcoma
Beryllium	In alloys, cathode ray tubes, ceramics, electrical equipment, gas mantles, missiles, nuclear reactors and refractory materials	Granulomas
Carbon tetrachloride	As degreasers, fat processors, fire extinguisher, fumigant, production of solvents; in fluorocarbons, ink, insecticides, lacquer, propellants, refrigerants, rubber and wax	Acute injury and death of parenchymal cells; ? cirrhosis; ? carcinoma
Dimethylacetamide	As solvent	Acute injury and death of parenchymal cells
Dimethylformamide	As solvent, in manufacture of butadiene, drugs, dyes, petroleum resins, synthetic fibers	Acute injury and death of parenchymal cells
Dimethylnitrosamine	As solvent and in rocket fuel; in cancer research	Acute injury and death of parenchymal cells; ? carcinoma
Dioxane	As solvent, degreaser, cement component; in production of adhesives, deodorants, detergents, emulsions, fats, glue, lacquer, oil, paint, polish, shoe cream, varnish remover, waxes; in histology laboratories	Subacute injury of parenchymal cells
Pentachloronaphthalene	In electric wire insulation and some lubricants	Acute injury and death of parenchymal cells
Phosphorus (yellow)	In munitions, pyrotechnics, explosives, smoke bombs, fertilizers, rodenticides, bronze alloys, semiconductors, luminescent coatings and chemical manufacture	Acute injury and death of parenchymal cells
Picric acid (2,4,6-trinitrophenol)	As copper etcher, forensic and biology laboratory chemical; in batteries, colored glass, disinfectants, drugs, dyes, explosives, matches, photography chemicals and tanneries	Acute injury and death of parenchymal cells
Polychlorinated biphenyls	In cable insulation, dyes, electric equipment, herbicides, lacquers, paper treatment, plasticizers, resins, rubber, textiles, flameproofers, transformers, and wood preservation	Subacute injury of parenchymal cells, proliferation of smooth endoplasmic reticulum; ? cirrhosis; ? carcinoma
sym-Tetrabromoethane (acetylene tetrabromide)	As solvent and gauge fluid; refractive index liquid in microscopy	Acute injury and death of parenchymal cells
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Contaminant of commercial preparations of 2,4,5-trichlorophenoxyacetic acid, polychlorinated biphenyls and other chlorinated compounds	Porphyria cutanea tarda; proliferation of small endoplasmic reticulum and some forms of associated monooxygenase enzymes
Tetrachloroethane	As dry-cleaning agent, fumigant, solvent, degreaser; in production of gaskets, lacquers, paints, phosphorus, resins, varnish, wax	Acute injury and death of parenchymal cells
Tetrachloroethylene	As solvent, degreaser, chemical intermediate, fumigant; in production of cellulose esters, gums, rubber, soap, vacuum tubes, wax, wool	Acute injury and death of parenchymal cells
2,4,5-Trinitrotoluene	As explosive	Acute and subacute injury and death of parenchymal cells
Vinyl chloride	As chemical intermediate and solvent; in production of polyvinyl chloride and resins	Fibrosis, noncirrhotic portal hypertension, cirrhosis, angiosarcoma, carcinoma

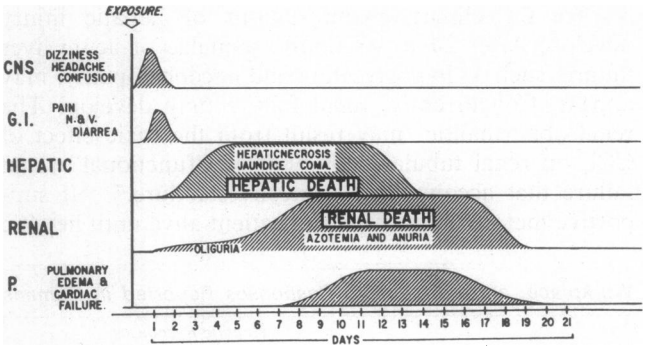

Figure 1.—Clinical sequence in acute carbon tetrachloride poisoning. (Reproduced with permission of the author and publisher from Zimmerman.[22])

and renal tubular cells regenerate, the ultimate prognosis for complete recovery is excellent, similar to the prognosis after acute ingestion of the hepatotoxin acetaminophen.

Whether or not there are any "antidotes" to acute CCl_4-induced hepatotoxicity in humans has not been established. Successful treatment with hyperbaric oxygen was reported recently in one patient, together with some experimental data in animals to support this form of therapy.[24] However, the therapy is by no means proved and in no way replaces full supportive care for hepatic and renal failure. Animals can be protected in several other ways from CCl_4-induced hepatotoxicity. For example, 16,16-dimethyl prostaglandin E,[25] chlorpromazine,[26] and cholestyramine and biliary diversion[27] protect against acute hepatic necrosis. These therapies have not yet been applied to humans.

Enhancement of the P-450 metabolism of CCl_4 by ethanol is one explanation for the well-documented synergistic effect between ethanol abuse and CCl_4 in humans.[6] Ethanol intake has been a concomitant factor in many of the human cases of CCl_4-induced hepatotoxicity, particularly in patients in whom both severe liver and kidney damage developed.[23] However, single doses of ethanol,[28] as well as other types of alcohol such as isopropyl alcohol,[29] also potentiate CCl_4 hepatotoxicity in animals. These potentiations must be due to other mechanisms.

Only anecdotal case reports have been presented as evidence that continuous exposure to CCl_4 causes cirrhosis.[3,5] However, this possibility is a cause for concern, particularly when one considers the synergistic effect of ethanol consumption on CCl_4-induced hepatotoxicity. Would hepatic cirrhosis be more likely to develop in persons who consume ethanol if they are exposed to a halogenated aliphatic hydrocarbon such as CCl_4 in the workplace? The answer is not known.

Again, only anecdotal reports suggest that CCl_4 can produce hepatocellular carcinoma in humans.[3,5] The evidence is still not sufficient to prove an association between the compound and hepatocellular carcinoma. However, in a retrospective study of causes of death in 330 deceased laundry and dry-cleaning workers who had been exposed to CCl_4, trichloroethylene and tetrachoroethylene, an excessive incidence of lung, cervical and skin cancer and a slightly excessive incidence of leukemias and liver cancer were observed.[30] The International Agency on Research in Cancer recommends that for practical purposes CCl_4 be regarded as a carcinogenic risk to humans.[5]

Vinyl Chloride

The fear that vinyl chloride might produce chronic liver disease and malignant tumors has been realized. As with CCl_4, a review of this chemical's toxicity highlights principles that apply to the toxicology of many workplace chemicals. Several reviews of its use and toxicity are available.[31-33]

Like CCl_4, vinyl chloride is a halogenated aliphatic compound. It is a colorless gas but is usually handled as a liquid under pressure. It is used in the production of resins such as polyvinyl chloride, as a chemical intermediate, as a component of propellant mixtures and as a solvent. The OSHA standard now sets a limit of 1 ppm over an eight-hour period and a ceiling of 5 ppm averaged over any period less than 15 minutes. However, problems with vinyl chloride were encountered before the permissible exposure limits were set. The recognition that an unusual type of hepatic fibrosis as well as angiosarcoma of the liver developed in persons who worked with vinyl chloride came after more than 30 years of steadily increasing production and use of enormous quantities of vinyl chloride.

Engineering surveys demonstrated that hundreds of thousands of workers had been exposed to high concentrations of vinyl chloride at various stages of its industrial production and use. Polymerization of the monomer vinyl chloride produces polyvinyl chloride, which is made into commercial or consumer products such as plastic pipe and conduit, floor cover, food wrap, and building and car interiors. These products may contain quite high concentrations of the residual monomer. In many polymers the residual monomer was present at 1,000 to 5,000 ppm by weight.[33]

Not only were workers engaged in the production of polyvinyl chloride or the use of vinyl chloride exposed to the concentrations of the compound, but also residents in areas near factories, people using vinyl chloride propellant sprays and possibly populations consuming food contained in plastics made with vinyl chloride. Vinyl chloride was also found in concentrations of 0.4 to 1.2 ppm in new automobile interiors. Vinyl chloride has been detected in cigarettes in concentrations of 5.6 to 27 nanograms per cigarette.[33]

It is instructive to examine in retrospect the information reported about the biologic effects of vinyl chloride.[34] Acute toxicity from vinyl chloride in guinea pigs, mice and dogs was reported in 1938. A report of cases of liver damage from vinyl chloride in humans was published in 1949. In 1961 chronic toxicity studies in several animal species showed that vinyl chloride at concentrations in the air above 50 ppm produced liver damage. Acroosteolysis, an unusual disease in humans, was associated with exposure to vinyl chloride in 1966. This disease is characterized by dissolution of the bones of the fingers and toes and vascular changes producing Raynaud's phenomenon. In

1970 the development of cancer in skin, lung and bones of rats exposed to vinyl chloride was reported. It was not until January 1974 that great interest in the compound was aroused. In that year a manufacturer of polyvinyl chloride and other polymers notified the public and appropriate state and federal agencies that three employees had died from angiosarcoma of the liver.[35] This tumor was unusual enough to make the association between vinyl chloride exposure and the tumor noticeable in such a small sample. The three employees had been exposed to vinyl chloride for up to 20 years. An immediate survey by NIOSH and similar agencies in other countries that used vinyl chloride confirmed the association between exposure to vinyl chloride monomer and development of this type of tumor and identified scores of cases.[36] These studies also found a consistent association between vinyl chloride exposure and tumors in sites other than the liver, not only in employees but also in populations living in areas surrounding vinyl chloride polymerization plants.[31] Angiosarcomas in vinyl chloride workers and animals were recognized virtually simultaneously.[31]

Similar to CCl_4, one mechanism of toxicity of vinyl chloride is through its metabolism by the cytochrome P-450 system to electrophilic intermediates. These intermediates react with nucleophiles (electron-rich donors) that either detoxify the intermediates or are critical cellular components. Detailed reviews of the pathologic lesions in animals and humans are available.[31]

Exposure of humans to vinyl chloride is associated with multiple systemic diseases including acroosteolysis, thrombocytopenia and liver damage. The latter can consist of parenchymal damage, fibrosis of the liver capsule and periportal fibrosis associated with hepatomegaly and splenomegaly, portal hypertension, hepatocellular carcinoma and angiosarcoma. Exposure to thorium dioxide (Thorotrast), a radiocontrast dye that is no longer used, and to inorganic arsenicals may be followed by development of the same tumors.[37] Arsenicals also produce the peculiar hepatic fibrosis associated with portal hypertension. Both vinyl chloride and the arsenicals induce proliferation of parenchymal and endothelial cells. Early abnormalities include sinusoidal dilation progressing to peliosis (blood-filled lakes within the liver lobule) and sarcomatous transformation of the lining cells of sinusoids and portal capillaries. Similar forms of sinusoidal dilation without angiosarcoma occur in women taking oral contraceptives and in men and women receiving large doses of anabolic steroids.[37]

Angiosarcoma of the liver is usually not recognized until within a few months of death. Whether or not earlier alterations in hepatic structure might be reversible if exposure to vinyl chloride is stopped is not known. An employee who is or was exposed to vinyl chloride in concentrations in excess of the now-recommended standard should have a complete history taken, including a history of liver disease and history of exposure to other potential hepatotoxic agents including alcohol, and a complete physical examination.[38] The full evaluation should be repeated every six months for an em-

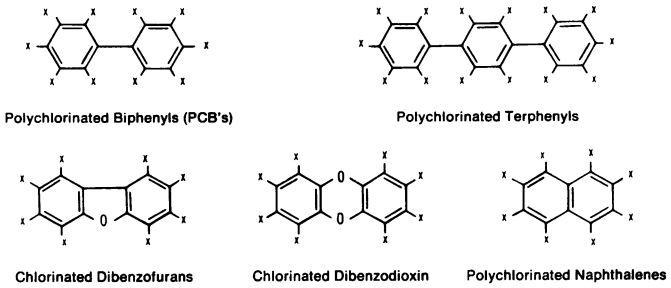

Figure 2.—General structure of polychlorinated biphenyls (PCB's), terphenyls, dibenzofurans, dibenzodioxins, and naphthalenes. X represents possible chlorine substituent. (Reproduced with permission of the author and publisher from Kimbrough.[40])

ployee who has been working in vinyl chloride or polyvinyl chloride manufacturing for ten years or longer, and annually for all other employees. The liver function tests and bilirubin, alkaline phosphatase, serum aminotransferase and γ-glutamyl transpeptidase determinations should be done at the same time. If data suggest the presence of hepatic involvement, ultrasonography[39] or computerized tomographic scanning of the liver should probably be carried out to look for hepatic tumors.

The experience with vinyl chloride highlights two principles paramount in occupational medicine—that occupational disease from some chemicals can be predicted in animal bioassays and that positive human epidemiologic data should not be necessary to conclude that a chemical poses a human risk. In contrast to our experience with vinyl chloride, the next chemicals discussed, the polychlorinated biphenyls (PCB's), provide an example in which production and use of the chemicals are being restricted in the workplace because of toxicities observed in experimental animals.

Polychlorinated Biphenyls

Biphenyl can be chlorinated by replacing one or more of its hydrogen atoms with chlorine. In the commercial synthesis of chlorobiphenyls, isomeric mixtures are produced that are referred to as polychlorinated biphenyls or PCB's. The biphenyl molecule, the numbering system and two examples of chlorobiphenyl compounds are shown in Figure 2.[40] Several reviews of their use and toxicity are available.[40-43] One common trade name under which commercial products have been marketed is Aroclor. The grades of Aroclor are designated by numbers such as 2521, 1221 and 1242. The last two numbers designate the percent by weight of chlorine in the mixtures. The first two digits indicate the type of product; for example, 12 equals chlorinated biphenyls and 25 equals blend of chlorinated biphenyls and chlorinated triphenyls. Commercial PCB products also contain contaminants such as dibenzofurans and naphthalenes (Figure 2). These impurities, which are often more biologically active than the PCB's themselves, have made interpretation of many epidemiologic studies of the toxicity of PCB's difficult.

Polychlorinated biphenyls were first produced commercially in the United States in 1929.[42] In 1970 pro-

duction had reached 80 million kg, and from 1929 through 1970 approximately 454 million kg of PCB's had been sold in North America. A second large commercial producer of PCB's, Japan, began production in 1954. By the end of 1971 approximately 54.4 million kg had been produced in that country; about 60 percent was exported to the United States and the remaining 40 percent was exported to Europe. The excellent thermal and chemical stability of PCB's led to their widespread use as insulating liquids in electrical capacitors, transformers and nuclear reactors and much of the accessory equipment. In addition, before 1971 PCB's were used in plasticizers, hydraulic fluids and lubricants, surface coatings, inks, sealants, adhesives, carbonless copy paper, pesticide extenders, for microencapsulation of dyes and as microscope immersion oils. These uses led to loss of about 40 percent of the PCB's into the environment. In the United States in 1971 the sole producer of PCB's limited their use to closed electrical systems so that release to the environment could be minimized.

Large-scale PCB contamination of cooking oil in Japan,[43] the death of 400,000 chickens in Japan from eating contaminated feed and destruction of 75,000 eggs in North Carolina because of contaminated chicken feed (400 ppm of PCB's)[44] led in part to voluntary restriction in the method of using these compounds. It had also become evident by 1968 that over the period of production and use since 1929, PCB's had become constituents of the human body. They persisted in the environment, accumulated in living tissue and were concentrated or biomagnified in the food chain,[40-42,44] similar to other organochlorine compounds such as the pesticide DDT. Many reports established "background" concentrations of PCB's in blood and tissues of human populations that had no occupational exposure to PCB's. Detectable residues were typically found in more than 50 percent of the persons tested and residues were found in human milk in several countries of Europe, North America and Asia. The reasons for the accumulation in tissues are that, like other heavy chlorinated compounds, PCB's are metabolized slowly, primarily in the liver, by hydroxylation and conjugation with glucuronic acid. Because of their lipophilicity, the major storage tissues for PCB are fat and liver. Apart from environmental contamination, PCB's had been proved to be carcinogens and had produced a number of other disturbing toxicities in animals. In 1976 the US Environmental Protection Agency banned the manufacture and sale of equipment containing PCB's and required the labeling of any existing equipment containing large quantities. As this equipment comes up for repair, the PCB's should be drained and replaced with a non-PCB oil. Now, NIOSH recommends an occupational environmental limit of 1.0 μg of total PCB's per cu meter of air and has outlined strict work practices for their handling and use.[45]

The PCB's have an extremely low acute toxicity in all animal species. The acute oral lethal dose for 50 percent survival in rodents given PCB's ranges from 1 to 10 grams per kg of body weight.

However, the array of adverse effects from chronic exposure to relatively low doses of PCB's observed consistently in animals includes acute and subacute hepatocellular toxicity, induction of the cytochrome P-450 system, induction of mitochondrial aminolevulinate synthetase producing various forms of porphyria, and endocrine, reproductive and immunologic abnormalities.[40-42,44]

The major changes in the liver of rodents fed PCB's chronically include enlarged livers, accumulation of lipid, proliferation of the smooth endoplasmic reticulum in the cytoplasm of centrilobular liver cells, fibrosis of bile ducts, and development of adenomas and carcinomas. The smooth endoplasmic reticulum contains the cytochrome P-450 system imbedded in lipid membranes. The PCB mixtures, powerful inducers of several forms of cytochrome P-450,[46] increase the activity of enzymes that metabolize drugs or environmental chemicals, including many chemical carcinogens. For example, in the Ames *Salmonella*/microsome mutagenicity test, the test bacteria are mixed with the microsomal fraction of rat liver. The liver activates many carcinogens by metabolism. To enhance the sensitivity of the test, the rats are pretreated with Aroclor 1254 or phenobarbital so that the P-450 metabolism of the carcinogens by the microsomal fraction is enhanced.[47] In animals, PCB's can potentiate the hepatic and renal toxicity of CCl_4 and other chlorinated hydrocarbons by enhancing their metabolism.[48]

As already mentioned, the PCB's are themselves mutagenic and carcinogenic in animals.[41] The predominant tumors are hepatocellular carcinomas. The carcinogenicity probably arises from metabolic products produced during the metabolism of PCB's by the cytochrome P-450 system. Primates are even more susceptible to development of PCB toxicities than rodents. The reasons for concern about the potential of PCB's to be carcinogens or to enhance the carcinogenicity of other workplace chemicals are obvious.

Polychlorinated biphenyls ingested in rice oil produced a serious human epidemic illness in Japan.[43] More than 300 patients became ill after ingesting a brand of rice bran oil contaminated with PCB's. The PCB's had leaked through the heat exchange unit used to heat the oil to remove odorous impurities before shipping. The PCB's were themselves contaminated with polychlorinated dibenzofurans and naphthalenes. The incident was referred to as the Yusho (oil disease) epidemic. The oil used for frying food, which may have altered the contaminating chemicals even further, was consumed from May through October 1968 and the first patient sought medical attention in June 1968. The health effects observed in that and other patients were chloracne, chromodermatosis, swelling of the upper eyelids and conjunctivitis, peripheral neuropathy and congenital abnormalities in babies born to women with Yusho. One report described a baby in whom Yusho developed from the PCB's contaminating breast milk. Of the patients examined early during the epidemic, 11 percent were jaundiced. The Yusho patients are now being followed to evaluate the potential of PCB's as

human carcinogens. However, how much the health effects observed in the Yusho epidemic can be extrapolated to occupational exposure is not clear for the following reasons. These people ingested a large amount of PCB's as opposed to inhaling or absorbing them through the skin. The exact chemical composition of the Yusho PCB's and their impurities is not known, except that dibenzofuran concentrations were high. Furthermore, frying of foods with rice oil could have produced new compounds that had their own toxicity or altered the toxicity of PCB's or their contaminants.

The health effects observed consistently in people exposed chronically to PCB's in the workplace are chloracne, contact or allergic dermatitis and brown chromodermatosis.[41,44] Reports from 1954 through 1976 noted abnormal liver function test findings in PCB-exposed workers. However, these studies did not control well for other chemical exposures, alcohol intake or other diseases. In 1981 Maroni and co-workers reported a study of 80 workers who were exposed to PCB's in a plant manufacturing electrical capacitors and transformers.[49,50] They measured PCB levels in the air and on the surfaces of machinery and tools and found that air concentrations were high. The major route of systemic exposure to PCB's was from percutaneous absorption of the chemicals. These investigators detected 16 people who had "pronounced hepatic involvement," determined from symptoms, clinical examination and laboratory tests. None underwent a liver biopsy. The 16 all were men and none had a history of excessive intake of alcohol or drugs. These data indicate that hepatic injury in humans from long-term exposure to PCB's should be regarded as a clinical problem. Alvares and co-workers[51] studied five persons who were occupationally exposed to Arochlor-1016 in a capacitor-manufacturing plant and showed that the clearance of antipyrine, a drug metabolized by the cytochrome P-450 system, was greater and the half-life of elimination shorter in these people than in non-PCB-exposed normal subjects. These data indicate that PCB's enhance the activity of the P-450 system in humans, probably by increasing liver content of the enzymes, in much the same way that they are potent inducers of cytochrome P-450's in animals.

Retrospective epidemiologic studies have not detected a significant excess of deaths from cirrhosis of the liver or carcinoma or reproductive effects in workers exposed for a long time to PCB's. However, the findings are not regarded as complete and prospective epidemiologic studies are still continuing. In view of the persistence of PCB's in the environment and in the body, and the irreversibility of some of their effects in animals, all attempts are being made to keep human exposure to PCB's at the lowest possible levels.

What should be done for a person who is exposed acutely to PCB's? For example, what measures would be appropriate if a capacitor exploded and a worker were drenched in oil? Immediate health effects are unlikely. However, the PCB's are absorbed easily through the skin and lungs. In such a case, the victim should remove all clothing, seal clothes in plastic bags and wash the skin thoroughly. If the eyes are contaminated, they should be flushed with water for 15 minutes. The spill area should be roped off to prevent anyone except those involved in the clean-up from entering. Appropriate local agencies should be contacted for information about the clean-up of the spill and disposal, storage and transportation of PCB's. Symptoms or signs of skin manifestations will be the first indication of PCB toxicity if the acute exposure was sufficiently massive. Because of the variation in background concentrations of PCB's between people, measuring blood or fat concentrations of PCB's to predict long-term toxicity is of no value.

Conclusions

This review has concentrated on compounds that appear to single out the liver as their target organ for toxicity. Many compounds do fall into this category, but the reader should remember that hepatotoxicity may be only one facet of a chemical's adverse effects. The sensitivity of the liver to the toxic effects of a chemical should warn physicians that other organs may also be affected. In animal studies the liver may be the first site of an injury that manifests in other organs as well. In humans the pesticide chlordecone not only produced hepatic injury but also neurologic and reproductive abnormalities.[52] Finally, 2-naphthylamine produces hepatocellular carcinoma in mice but bladder carcinoma in humans.[53] Thus, a chemical that produces its effects in the liver in animals, may manifest its toxicity elsewhere in humans.

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